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GUIDELINES / CLINICAL TRIALS/META-ANALYSIS (WJ KOSTIS, SECTION EDITOR)

Renin-Angiotensin System Inhibitors and COVID-19: a Systematic Review and Meta-Analysis. Evidence for Significant Geographical Disparities

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Abstract

Purpose of Review While the COVID-19 pandemic is constantly evolving, it remains unclear whether the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) affects the clinical course of SARS-CoV-2 infection. For this meta-analysis, PubMed, CENTRAL, and grey literature were searched from their inception to 19 May 2020 for randomized, controlled trials or observational studies that evaluate the association between the use of either ACE inhibitors or ARBs and the risk for major clinical endpoints (infection, hospitalization, admission to ICU, death) in adult patients during the COVID-19 pandemic. In addition, a subgroup geographical analysis of outcomes was performed. Studies including less than 100 subjects were excluded from our analysis.

Recent Findings In total, 25 observational studies were included. ACE inhibitors and ARBs were not associated with increased odds for SARS-CoV-2 infection, admission to hospital, severe or critical illness, admission to ICU, and SARS-CoV-2-related death. In Asian countries, the use of ACE inhibitors/ARBs decreased the odds for severe or critical illness and death (OR = 0.37, 95% CI 0.16–0.89, $I^2 = 83\%$, and OR = 0.62, 95% CI 0.39–0.99, $I^2 = 0\%$, respectively), whereas they increased the odds for ICU admission in North America and death in Europe (OR = 1.75, 95% CI 1.37–2.23, $I^2 = 0\%$, and OR = 1.68, 95% CI 1.05–2.70, $I^2 = 82\%$, respectively). ACE inhibitors might be marginally protective regarding SARS-CoV-2-related death compared with ARBs (OR = 0.86, 95% CI 0.74–1.00, $I^2 = 0\%$).

Summary Randomized controlled trials are needed to confirm the aforementioned associations between ACE inhibitors, ARBs, and SARS-CoV-2.

Keywords SARS-CoV-2 · COVID-19 · Hypertension · Angiotensin-converting enzyme inhibitors · ACE inhibitors · Angiotensin receptor blockers · ARBs · Renin-angiotensin inhibitors · RAS inhibitors

Introduction

Last December, a novel coronavirus contaminated a first cluster of Chinese patients in Wuhan [1]. A severe acute respiratory syndrome coronavirus (SARS-CoV)-2 has spread rapidly around the globe reaching a pandemic status during the first trimester of 2020. Currently, the coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2, accounts for more than 5,500,000 cases and 350,000 deaths worldwide, along with unprecedented detrimental effects on healthcare systems and global economy [2]. Therefore, widespread intense efforts are applied to better understandCOVID-19 and expand our knowledge in several clinically meaningful aspects.

This article is part of the Topical Collection on *Guidelines / Clinical Trials/Meta-Analysis*

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Initial reports demonstrated that similar to the previous SARS-CoV, the novel SARS-CoV-2 employs angiotensin-converting enzyme 2 (ACE2) as the receptor to infect human cells through its spike protein [3, 4]. Consequently, this specific interaction has been postulated as a potential factor in SARS-CoV-2 infectivity [5], and concerns were generated about the use of renin-angiotensin (RAS) inhibitors in patients with hypertension, diabetes mellitus, and cardiovascular disease [6–9]. Indeed, some media sources, health systems, and scientists suggested the discontinuation of RAS inhibitors, until more data is available.

However, an abundance of clinical data in millions of patients robustly documents that RAS inhibitors provide significant benefits in patients with cardiovascular disease. In brief, RAS inhibitors reduce major cardiovascular adverse events and mortality in a wide cluster of diseases, such as hypertension, myocardial infarction, cerebrovascular disease, heart failure with reduced ejection fraction, left ventricular hypertrophy, and albuminuria [10, 11]. Consequently, withdrawal of RAS inhibitors in those very high-risk patients might result in clinical instability and adverse health outcomes, which in turn might increase both mortality and the need of hospitalization during the pandemic, when healthcare systems are highly overwhelmed.

Altogether, the use of RAS inhibitors emerged as a fundamental health issue in COVID-19 pandemic, but existing data—either experimental or clinical—seems pretty conflicting and scarce. Towards this end, we conducted a systematic review and meta-analysis of clinical studies assessing the association of RAS inhibitors with COVID-19 infectivity, severity (need for hospitalization, admission to intensive care unit (ICU)), and mortality. We also sought to unveil potential differences between angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in these outcomes, as well as potential disparities in different continents.

Systematic Review and Meta-Analysis

Methods

This systematic review and meta-analysis are reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [12].

Eligibility Criteria

We searched for available randomized controlled trials or observational studies, regardless of study duration, enrolling adult patients, and evaluating the association between the use of either ACE inhibitors or ARBs and the risk (or odds) for major clinical endpoints in the context of infection from SARS-CoV-2 during the COVID-19 pandemic. We planned to exclude studies enrolling patients aged less than 18 years and studies including less than 100 subjects.

We did not implement any restriction regarding study setting.

Search Strategy

We performed a systematic search in two major electronic databases, PubMed and Cochrane Central Register of Controlled Trials (CENTRAL), from their inception to 19 May 2020. MeSH terms were used for both therapeutic interventions, along with free-text words. We also used the Boolean operators "OR" and "AND." Our search was therefore restricted to human studies. We did not impose any filter regarding language, text availability, and publication date. Search strategy in the two major databases is provided in supplementary appendix (supplementary tables 1 and 2).

Grey literature was searched, as well. We searched the clinicaltrials.gov (supplementary table 3) and the medRxiv.org from inception to 19 May 2020. Reference lists of all eligible studies were handsearched, as well. Search strategy was reviewed upon the PRESS 2015 Guideline Statement [13].

Finally, we planned to contact authors of identified studies for retrieving missing or unclear data.

Study Selection

All retrieved reports were imported into reference software manager (Mendeley©) for deduplication. After that, remaining reports were reviewed at title and abstract level by two independent reviewers (D.P. and A.K.). Potentially eligible studies were full-text assessed. Any discrepancies among the two reviewers at any stage were resolved by discussion, consensus, or arbitration by a third senior reviewer (M.D.). Eligible reports from grey literature were cross-checked with the results retrieved from electronic databases. The study selection process is depicted in the corresponding flow diagram (Fig. 1).

Data Extraction

Two independent reviewers (D.P. and A.K.) extracted the data from the eligible reports, by using a pilot tested, data extraction form developed in Microsoft Excel©.

Extracted information included the following: source characteristics, study characteristics, participants' baseline characteristics, interventions, and comparators (if any), along with key clinical outcomes. We defined the following major clinical endpoints as outcomes of our systematic review and meta-analysis:

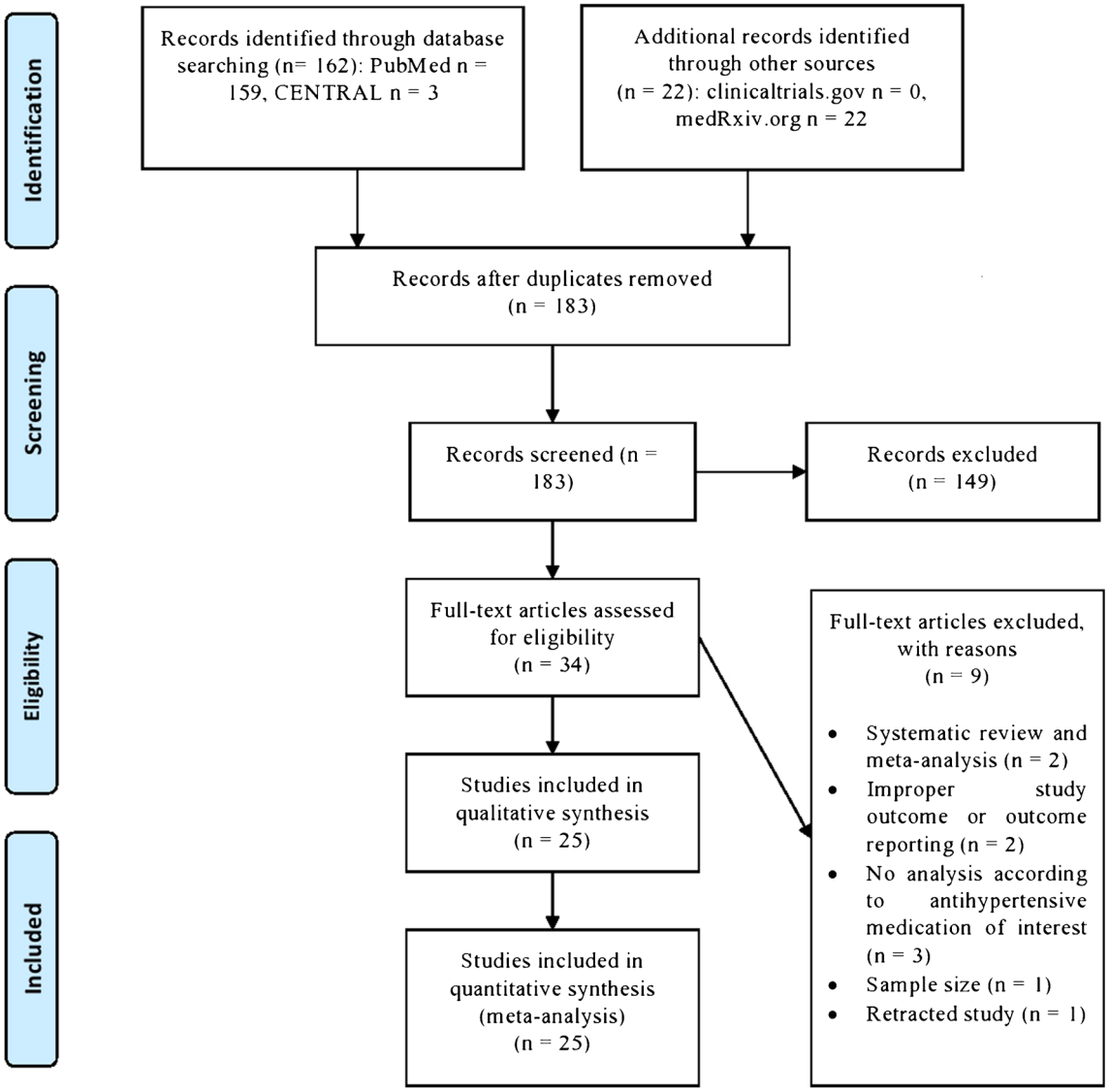


Fig. 1 Flow diagram depicting the study selection process

1. testing positive for SARS-CoV-2 (defined as primary outcome)
2. admission to hospital
3. development of severe or critical illness
4. admission to ICU
5. SARS-CoV-2-related death

If the results of a study were reported in multiple articles or at different follow-up time points, we preferred data extracted from journal articles, while we used the reports with the longest duration or the larger sample size.

We also planned to conduct additional subgroup analyses, if data were available, to assess the impact of RAS blockers on the aforementioned outcomes according to region (Asia, Europe, North America, etc.), gender, race/ethnicity, and main co-morbidities (cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic respiratory failure). We also evaluated the impact of ACE inhibitors vs. ARBs on outcomes of clinical interest (SARS-CoV-2-positive testing and related death, admission to ICU).

Risk of Bias Assessment

Two independent reviewers (D.P. and K.S.) assessed the quality of the included RCTs, by using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) [14]. Each domain was rated as low, unclear, or high risk of bias. Presence of adequate procedures in all domains rated a study as being of low risk of bias, while inadequate procedure in at least one domain rated a study as being of high risk of bias. The same reviewers assessed the quality of the included observational studies with the use of the Newcastle-Ottawa Scale (NOS) [15].The NOS assigns up to a maximum of 9 points for the risk of bias in 3 domains: (1) selection of study groups (4

Table 1 Summary characteristics of included studies

Study	Study type/country of origin	Study population	Male	Age	Diabetes mellitus	Hypertension	CVD	Use of ACEI/ARB
Bean et al. [18]	Retrospective cohort study/UK	1200 COVID-19 pt	57.2%	68	34.80%	53.80%	13.30% IHD, 8.9% HF	33.3% (21.7% on ACEi, 12.2% on ARB)
Benelli et al. [19]	Observational study/Italy	539 hospitalized pt (411 COVID-19 swab positive and 128 COVID-19 swab negative)	66.60% (swab positive)	66.8 (swab positive)	16.30% (swab positive)	47% (swab positive)	22.60% (swab positive)	12.2% on ACEi, 14.6% on ARB (swab positive)
Caraballo et al. [27]	Retrospective study/USA	900 tested pt (206 tested positive, 694 tested negative)	49.20%	73	-	73.90%	100% with HF, 29.9% with CAD	34.7% on ACEi/ARB
Chen et al. [34]	Retrospective study/China	904 COVID-19 pt	46.57%	56	15.04%	30.20%	10.07%	Among 71 hypertensive pt with available data: 45% on ACEi/ARB
Dauchet et al. [20]	Observational study/France	288 tested pt plus 1,569,968 and 414,046 controls	59% (outpatient), 59% (hospitalized), 69% (ICU)	49.7 (outpatient), 58.2 (hospitalized), 60.7 (ICU)	6% (outpatient), 15% (hospitalized), 26% (ICU)	19% (outpatient), 53% (hospitalized), 52% (ICU)	12% (outpatient), 23% (hospitalized), 21% (ICU)	On ACEi: 11% (outpatient), 23% (hospitalized), 15% (ICU); on ARB: 5% (outpatient), 13% (hospitalized), 24% (ICU)
De Abajo et al. [21]	Case-population study/Spain	1139 COVID-19 pt, 11,390 controls	61%	69.1	27.2% of cases, 20.3% of controls	54.2% of cases, 49.6% of controls	27.4% of cases, 21.1% of controls	On ACEi/ARB: 43.6% of cases, 33.6% of controls; on ACEi: 21.1% of cases, 19.2% of controls; on ARB: 21.4% of cases, 14.2% of controls
deSpiegeleer et al. [22]	Retrospective cohort study/Belgium	154 COVID-19 pt	33%	86	18.20%	25.30%	-	20% on ACEi/ARB (16% on ACEi, 4% on ARB)
Ebinger et al. [28]	Retrospective study/USA	442 COVID-19 pt	58%	52.7	19%	36%	11%	7% on ACEi, 9% on ARB
Feng et al. [35]	Retrospective study/China	476 COVID-19 pt	56.90%	53	10.30%	23.70%	8%	6.9% for ACEi/ARB (1.6% for ACEi, 5.6% of ARB)
Huh et al. [36]	Retrospective case-control study/Korea	5172 COVID-19 pt, 65,149 controls	49.40%	48.3	27.6%	32.8%	21.2% of controls, 15.5% of cases	On ACEi: 0.89% of cases, 1.01% of controls; on ARB: 12.92% of cases, 15.6% of controls
Ip et al. [29]	Retrospective study/USA	1584 hypertensive COVID-19 pt among 3017 cases	-	-	-	52.50%	-	Among hypertensive pt 22.8% on ACEi, 18% on ARB
Khawaja et al. [23]	Prospective cohort study/UK	406,188 controls, 605 COVID-19 pt	45%	68	5% of controls, 10% of cases	33% of controls, 48% of cases	IHD: 8% of controls, 15% of cases; stroke: 2% among controls, 5% among cases	On ACEi: 8% of controls, 14% of cases; on ARB: 4% of cases, 6% of controls
Khera et al. [30]	Observational study/USA	2263 outpatient COVID-19 pt, 7933 inpatient COVID-19 pt	outpatient cohort: 47.5%, inpatient	69 (outpatient), 77 (inpatient)	Outpatient: 67.9%, inpatient: 89.5%	100%	outpatient: 3.6% MI, 14.4% HF; inpatient: 5.4% MI, 31.1% HF	Outpatient: 31.9% on ACEi, 32.3% on ARB; inpatient: 29.76% on ACEi, 28.06% on ARB

Table 1 (continued)

Study	Study type/country of origin	Study population	Male	Age	Diabetes mellitus	Hypertension	CVD	Use of ACEI/ARB
			cohort: 45.4%					
Li et al. [37]	Retrospective study/China	1178 COVID-19 pt	52.20%	66	35.1% among hypertensive pt.	30.7%	17.1% among hypertensive pt	Among hypertensive pt: 9.7% on ACEi, 22.9% on ARB
Liu et al. [31]	Retrospective study/China	78 hypertensive pt among 511 COVID-19 pt	-	-	-	100%	-	Among elderly hypertensive patients ($n = 46$): 4.3% on ACEi, 21.7% on ARB
Mancia et al. [24]	Population-based case-controlled study/Italy	6272 COVID-19 pt, 30,759 controls	63%	68	On oral antidiabetic drugs: 13.7% of cases, 10.3% of controls; on insulin: 5.4% of cases, 2.8% of controls	57.9% of cases, 49.8% of controls	30.1% of cases, 21.7% of controls	On ACEi: 23.9% of cases, 21.4% of controls; on ARB: 22.2% of cases, 19.2% of controls
Mehta et al. [38]	Retrospective cohort study/USA	18,472 pt tested for COVID-19	40%	49	19%	40%	12% with CAD, 10% with HF	7.2% on ACEi, 5.3% on ARB
Meng et al. [43]	Retrospective study/China	417 COVID-19 pt	57.10%	64.5	-	100%	-	Among 42 hypertensive pt. on treatment: 40.4% on ACEi/ARB
Raisi et al. [25]	Observational study/UK	1474 tested pt, 501,032 controls	53.4% among COVID-19 tested pt	69.3	15.50%	49.40%	9.40%	21.2% on ACEi/ARB
Rentsch et al. [32]	Retrospective cohort study/USA	3789 pt tested for COVID-19	90.2%	65.7	37.8%	65%	28.9%	40.4% on ACEi/ARB (26.7% on ACEi, 14.9% on ARB)
Reynolds et al. [33]	Observational study/USA	12,594 pt tested for COVID-19	-	49	18%	34.6%	6.2% with HF and 4.2% with a history of MI	18.4% on ACEi/ARB (8.3% on ACEi, 10.5% on ARB)
Rossi et al. [26]	Population-based prospective cohort study/Italy	2653 COVID-19 pt	50.10%		12%	18.10%	7.10%	17% on ACEi, 13.9% on ARB
Yan et al. [39]	Observational study/China	610 COVID-19 pt, 48,667 controls	Cases: 51.1%, Controls: 48.3%	controls: 49.96, cases: 48.75	controls: 6.09%, cases: 9.84%	controls: 20.25%, cases: 22.46%	controls: 1.28%, cases: 2.62%	On ACEi: 1.14% of controls, 0.82% of cases; on ARB: 15.38% of controls, 8.69% of patients
Yang et al. [40]	Retrospective study/China	126 hypertensive COVID-19 pt plus 125 non-hypertensive COVID-19 pt	49%	66	Non-hypertensive: 13.6%, hypertensive: 30.2%	50.1%	Non-hypertensive: 9.6%, hypertensive: 18.3%	34.1% on ACEi/ARB
Zhou et al. [41]	Retrospective study/China	110 COVID-19 pt	54.5%	57.7	32.7%	10%	9.1%	41.6% of hypertensive pt on ACEi/ARB

ACEI angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *CAD* coronary artery disease, *CVD* cardiovascular disease, *HF* heart failure, *ICU* intensive care unit, *IHD* ischemic heart disease, *MI*: myocardial infraction, *pt* patients

points), (2) comparability of groups (2 points), and (3) ascertainment of exposure and outcomes (3 points) for case-control and cohort studies, respectively.

Discrepancies between reviewers were solved by discussion, consensus, or arbitration by a third senior reviewer (M.D.). Risk of bias assessment across the selected studies is provided in Table 2.

Data Synthesis and Analysis

Since we planned to assess major clinical endpoints representing dichotomous variables, differences were calculated with the use of odds ratio (OR), with 95% CI, after implementation of the Mantel-Haenszel (M-H) random effects formula. Statistical heterogeneity among studies was assessed by using I^2 statistics. Heterogeneity was considered to be low if I^2 was between 0 and 25%, moderate if I^2 was between 25 and 50%, or high if I^2 was greater than 75% [16].

All analyses were performed at the 0.05 significance level, while they were undertaken with the RevMan 5.3 software [17].

Results

We identified 183 records after implementing our search strategy in major databases and grey literature up to 19 May 2020. We assessed 34 full-text articles for potential inclusion in our systematic review and meta-analysis. After excluding 9 articles with reasons, including 2 previous systematic reviews and meta-analyses and a recently retracted paper, we ended up with 25 records to be included in our qualitative and quantitative synthesis. No completed randomized controlled trials were identified; thus, we included only observational studies in our synthesis.

Nine studies were conducted in Europe (UK, Italy, France, Spain, Belgium) [18–26], 7 studies took place in North America (the USA) [27–33], while 9 studies were conducted in Asia, mainly in China [31, 34–41]. Finally, we initially included in our quantitative synthesis a study utilizing data from an observational database from 169 hospitals in Asia, Europe, and North America, which was recently retracted and thus excluded from our analysis [42]. Summary of studies' characteristics is provided in Table 1, while quality assessment with the use of NOS is provided in Table 2.

Herein, we present the main findings of our quantitative synthesis.

ACE Inhibitors/ARBs vs. Non-ACE Inhibitors/ARBs and Outcomes of Clinical Significance

SARS-CoV-2 Testing Positive

Use of ACE inhibitors or ARBs is not associated with increased odds for testing positive for SARS-CoV-2 (OR = 0.99, 95% CI 0.83–1.17, $I^2 = 93\%$), as shown in Fig. 2a. Subgroup analysis according to region did not reveal any significant association between ACE inhibitors/ARBs use and SARS-CoV-2-positive testing (in Asia, OR = 0.76, 95% CI 0.54–1.07, $I^2 = 84\%$; in Europe, OR = 1.22, 95% CI 0.77–1.95, $I^2 = 97\%$; in North America, OR = 0.99, 95% CI 0.86–1.15, $I^2 = 62\%$). Inspection of the corresponding funnel plot for this primary outcome ruled out the presence of publication bias (supplementary figure 1).

Hospital Admission

Notably, use of ACE inhibitors or ARBs does not increase the odds for hospitalization in the context of SARS-CoV-2 infection (OR = 1.74, 95% CI 0.95–3.17, $I^2 = 96\%$), as depicted in Fig. 2b.

Severe or Critical Illness

Despite inconsistency in definitions and reporting across the included studies, it was observed that the use of either ACE

Table 2 Newcastle-Ottawa quality assessment Form regarding included studies

Study	Selection	Comparability	Outcome
Bean et al.	3	2	1
Benelli et al.	3	2	1
Caraballo et al.	3	2	1
Chen et al.	3	2	1
Dauchet et al.	3	2	1
De Abajo et al.	3	2	1
deSpiegeleer et al.	2	2	1
Ebinger et al.	2	2	1
Feng et al.	2	2	1
Huh et al.	3	2	0
Ip et al.	2	0	1
Khawaja et al.	3	2	1
Khera et al.	3	2	2
Li et al.	3	2	1
Liu et al.	2	0	1
Mancia et al.	3	2	1
Mehta et al.	3	2	1
Meng et al.	2	0	1
Raisi et al.	3	2	1
Rentsch et al.	3	2	1
Reynolds et al.	2	2	1
Rossi et al.	3	2	3
Yan et al.	3	2	1
Yang et al.	3	2	1
Zhou et al.	2	2	1

inhibitors or ARBs is not associated with increased odds for severe or critical illness (OR = 0.86, 95% CI 0.64–1.16, I^2 = 90%), as shown in Fig. 2c. Of note, use of ACE inhibitors/ARBs in Asia was associated with a significant reduction in the odds for severe or critical illness by 63% (OR = 0.37, 95% CI 0.16–0.89, I^2 = 83%), whereas, such an association was not shown in Europe (OR = 1.12, 95% CI 0.51–2.47, I^2 = 94%) and in North America (OR = 1.11, 95% CI 0.84–1.45, I^2 = 85%).

ICU Admission

It was also demonstrated that administration of ACE inhibitors or ARBs does not increase the odds for admission to ICU (OR = 1.40, 95% CI 0.80–2.43, I^2 = 86%), as shown in Fig. 2d. Notably, in subgroup analysis by region, it was shown that ACE inhibitors/ARBs use is associated with increased odds for ICU admission in North America (OR = 1.75, 95% CI 1.37–2.23, I^2 = 0%), while this association appeared non-significant in Europe (OR = 1.11, 95% CI 0.33–3.79, I^2 = 92%).

SARS-CoV-2-Related Death

Of note, use of ACE inhibitors or ARBs does not increase the odds for SARS-CoV-2-related death (OR = 1.06, 95% CI 0.63–1.43, I^2 = 83%), as depicted in Fig. 2e. However, in subgroup analysis by region, it was shown that ACE inhibitors/ARBs use increases the odds for death in Europe by 68% (OR = 1.68, 95% CI 1.05–2.70, I^2 = 82%), it decreases the corresponding odds in Asia by 38% (OR = 0.62, 95% CI 0.39–0.99, I^2 = 0%), whereas the association remains non-significant in the USA (OR = 0.95, 95% CI 0.63–1.43, I^2 = 84%).

Another Dilemma: ACE Inhibitors or ARBs

SARS-CoV-2 Testing Positive

No significant difference was detected in the odds for SARS-CoV-2-positive testing among users of ACE inhibitors or ARBs (OR = 0.96, 95% CI 0.87–1.05, I^2 = 38%), as shown in Fig. 3a. Notably, no significant difference was observed in the subgroup analysis by region (in Asia, OR = 1.08, 95% CI 0.81–1.45, I^2 = 0%; in Europe, OR = 0.91, 95% CI 0.73–1.14, I^2 = 68%; and in North America, OR = 1.01, 95% CI 0.90–1.12, I^2 = 0%).

Admission to ICU

No significant difference in the odds for admission to ICU between subjects receiving ACE inhibitors or ARBs was detected (OR = 0.73, 95% CI 0.35–1.56, I^2 = 43%), as depicted in Fig. 3b.

SARS-CoV-2-Related Death

Of interest, ACE inhibitors were found to be superior to ARBs in SARS-CoV-2-related death, although the result is marginally insignificant (OR = 0.86, 95% CI 0.74–1.00, I^2 = 0%), as shown in Fig. 3c.

Discussion

This is the first systematic review and meta-analysis of all available observational studies (published up to 19 May 2020), assessing the association of RAS inhibitors with the whole spectrum of COVID-19 (infection, hospitalization, severity, death), and also providing two very significant pieces of information: geographical variation and a comparison between ACE inhibitors and ARBs.

Ever since the evolution of this pandemic, ACE inhibitors and ARBs have been at the epicenter of attention, due to the connection of SARS-CoV-2 with ACE2, an enzyme that is implicated in the degradation of angiotensin II (Ang II) to Ang (1–7) and Ang I to Ang (1–9) resulting in reductions in blood pressure, vasodilation, increased renal sodium excretion, and suppression of inflammation [44]. ACE2 serves as a host receptor for SARS-CoV-2, and it was initially hypothesized that ACE inhibitors and ARBs could mediate SARS-CoV-2 infection through upregulation in ACE2 expression [6, 45]. However, at the same time, ACE2 could serve as a protective mechanism towards lung injury, through increased cleavage of Ang I and II with subsequent reduced vasoconstriction and inflammation [46]. Of note, our analysis demonstrated that ACE inhibitors/ARBs do not correlate with increased odds for SARS-CoV-2-positive testing, hospitalization, severe or critical illness, ICU admission, and death.

While the aforementioned findings regarding positive testing apply similarly to different regions, this is not the case for the rest outcomes. A reduction in the odds for severe or critical illness and death with the use of ACE inhibitors/ARBs was found for Asia and, on the contrary, use of ACE inhibitors/ARBs increased the odds for ICU admission in North America and related death in Europe. Could these generated differences be attributed to the different ethnic and racial composition of the population of the included studies? Central Asia has the highest burden of cardiovascular disease, when compared with Europe and North America [47], while racial differences have been reported among SARS-CoV-2-positive patients, such as that black race doubles the odds for

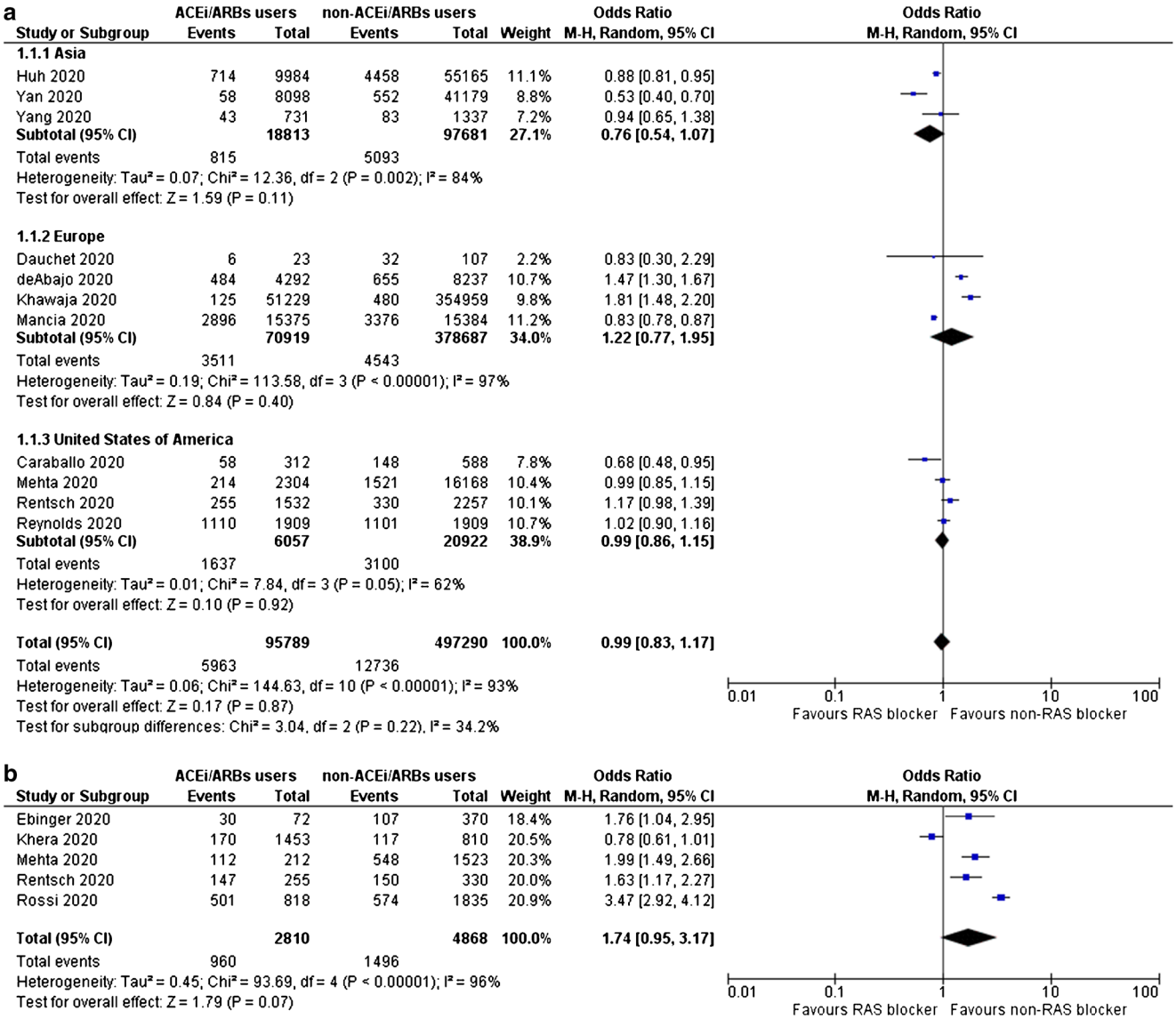


Fig. 2 **a** Odds for SARS-CoV-2-positive testing, **b** odds for admission to hospital, **c** odds for severe or critical illness, **d** odds for admission to ICU, and **e** odds for SARS-CoV-2-related death, for ACE inhibitors/ARBs users compared with non-users

hospital admission [48]. However, based on current evidence, it is unclear whether the use of ACE inhibitors or ARBs plays a role. Unfortunately, such a subgroup analysis could not be performed due to inadequate data reporting across the selected studies.

Another issue of concern is whether differences exist regarding SARS-CoV-2 infection outcomes among users of ACE inhibitors and ARBs. Alternate responses of ACE2 and Ang (1–7) were documented in an experimental model utilizing Lewis rats after the administration of lisinopril and losartan. More specifically, administration of an ACE inhibitor caused a 1.8 increase in Ang (1–7) and a 4.7-fold rise in cardiac ACE2 mRNA, although cardiac ACE2 activity remained unchanged. On the other hand, apart from Ang (1–7) and cardiac ACE2 mRNA, administration of an ARB increased cardiac ACE2 activity [49]. In our analysis, no significant differences were observed among ACE inhibitors and ARBs regarding odds for SARS-CoV-2-positive testing, ICU admission, and death, although there was an observed trend towards reduced odds for death with the use of ACE inhibitors. Nevertheless, results from ongoing phase 4 clinical trials that aim to assess the effects of losartan and valsartan on progression of acute respiratory distress syndrome are eagerly awaited (NCT04340557 and NCT04335786).

Two other meta-analyses have been published recently assessing the effects of ACE inhibitors and ARBs on mortality, critical or fatal outcome, and hospitalization. More specifically, Abdulhak et al. conducted a meta-analysis regarding the effects of ACE inhibitors/ARBs on mortality

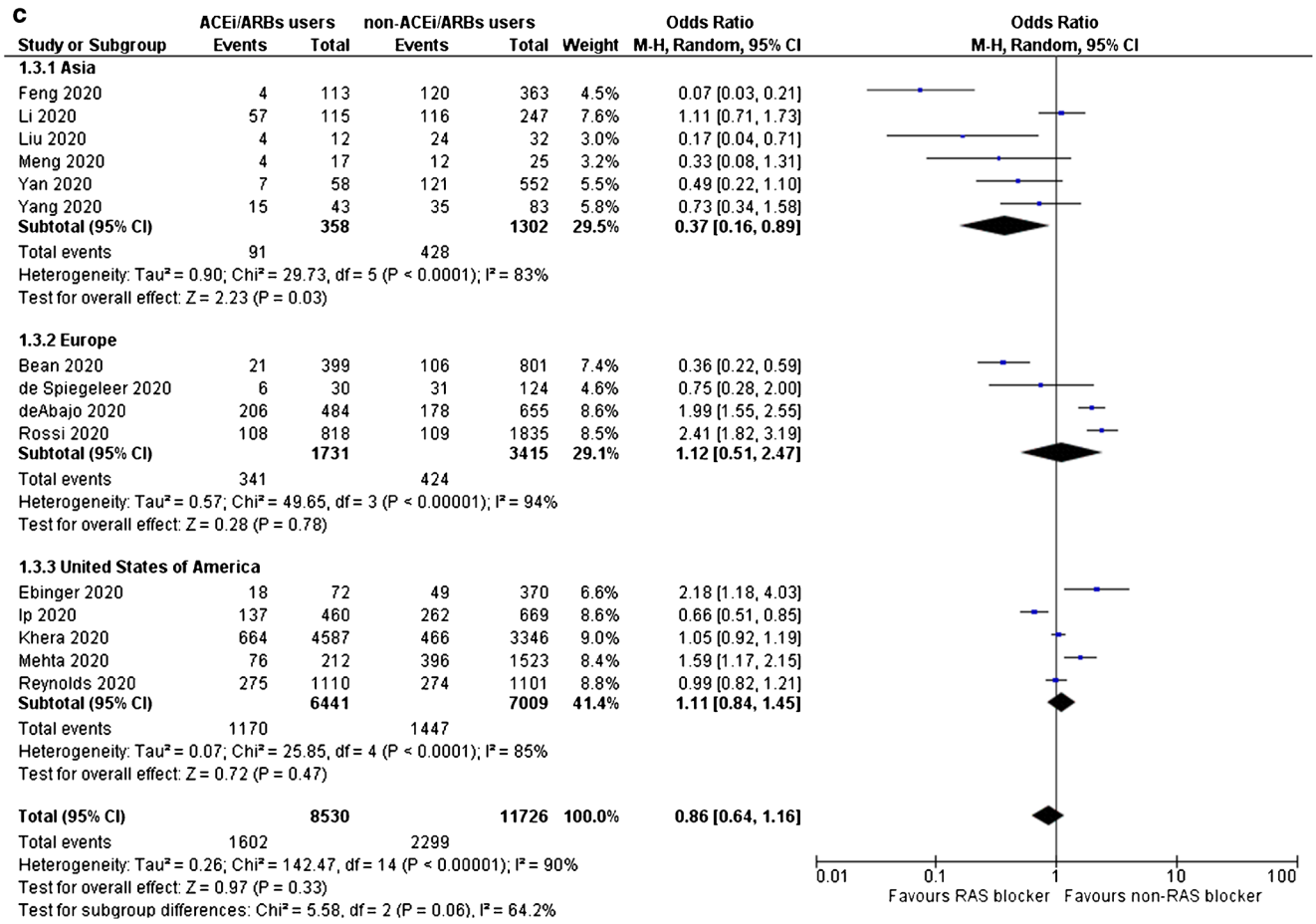


Fig. 2 (continued)

and a critical or fatal outcome. Interestingly, ACE inhibitors and ARBs were associated with reduced odds for inpatient mortality and a critical or fatal outcome (OR = 0.33, 95% CI 0.22–0.49, $I^2 = 0\%$, and OR = 0.32, 95% CI 0.22–0.46, $I^2 = 32\%$, respectively) [50]. Similarly, Ghosal et al. found a significant decrease in the odds for death with the use of ACE inhibitors/ARBs (OR = 0.57, 95% CI 0.37–0.88, $I^2 = 0\%$), while non-significant benefits were also observed in terms of developing severe disease or hospitalization (OR = 0.62, 95% CI 0.31–1.23, $I^2 = 70.36\%$, and OR = 0.81, 95% CI 0.42–1.55, $I^2 = 0\%$, respectively) [51]. Nevertheless, the former meta-analysis included five and the latter six studies, most of which were located in China. This could probably explain the reported different results among these and our meta-analysis, which included studies not only from China but also from Europe and North America, resulting in a larger sample size and enabling subgroup analysis among different continents.

Our meta-analysis has certain limitations. First, we included only observational studies; however, no randomized controlled studies are available so far. Forthcoming randomized controlled trials will shed further light on the association between ACE inhibitors/ARBs use and significant SARS-CoV-2-related clinical outcomes. Such RCTs are under way, after a thorough research of grey literature sources (ClinicalTrials.gov Identifier: NCT04353596, NCT04364893, NCT04345406, NCT04351581, NCT04338009, NCT04329195, NCT04493359, NCT04510662, NCT04366050, NCT04351724, NCT04355429), while some of them have been unfortunately suspended (ClinicalTrials.gov Identifier: NCT04330300). Second, heterogeneity is considered as high for most assessed outcomes; however, alternate pooling methods (switching from random to fixed effects formula) did not affect generated results. Finally, inconsistency of outcomes' reporting and selected definitions across the included studies did not permit us to perform subgroup analyses according to gender (male/female), race (white, black, Asian, other), or pre-existing co-morbidities (cardiovascular disease, chronic kidney disease, chronic respiratory failure, diabetes mellitus). The aforementioned constituted the investigation of sources of heterogeneity on outcomes of interest inevitable, potentially limiting the applicability of our results on general clinical practice.

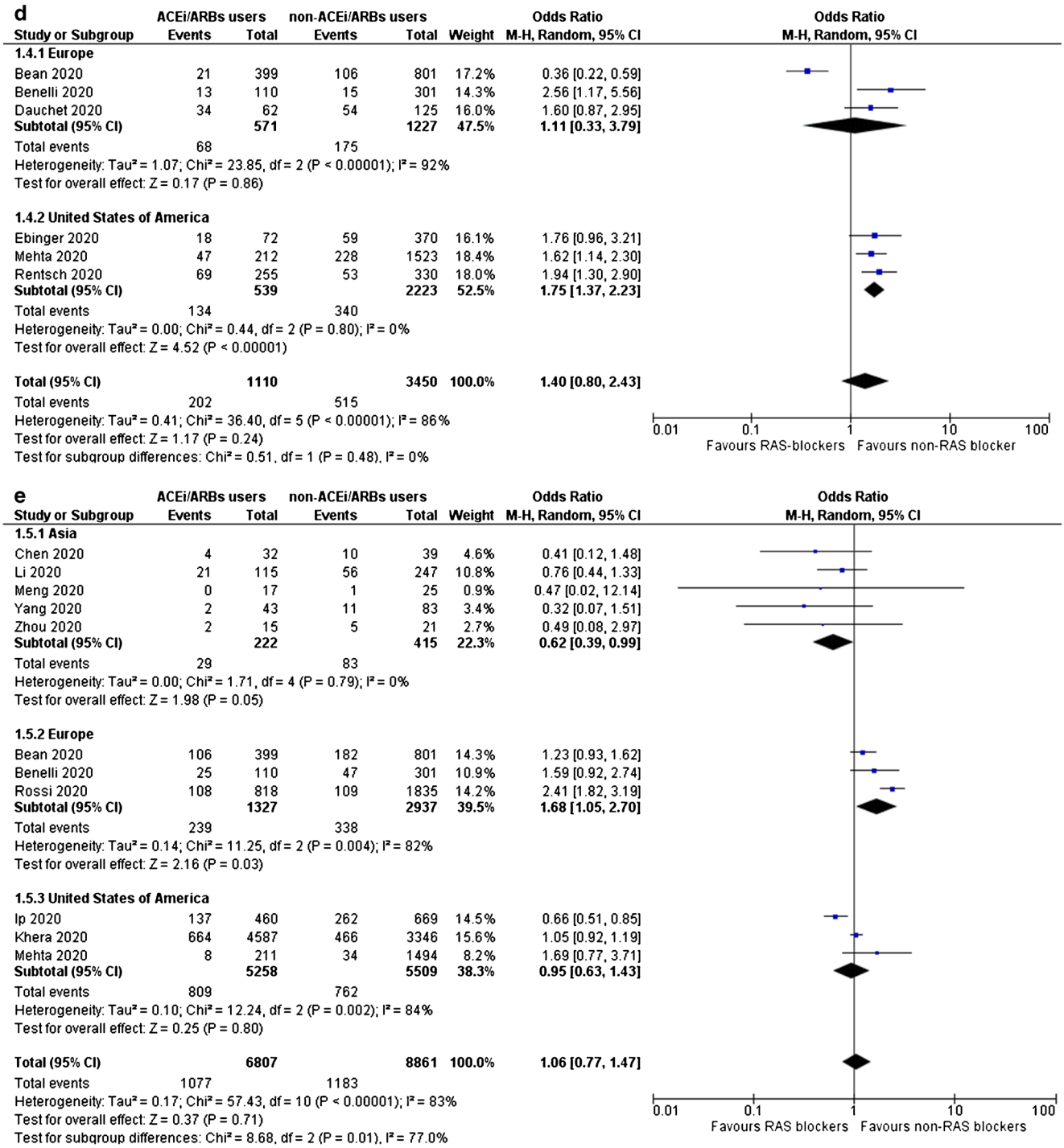


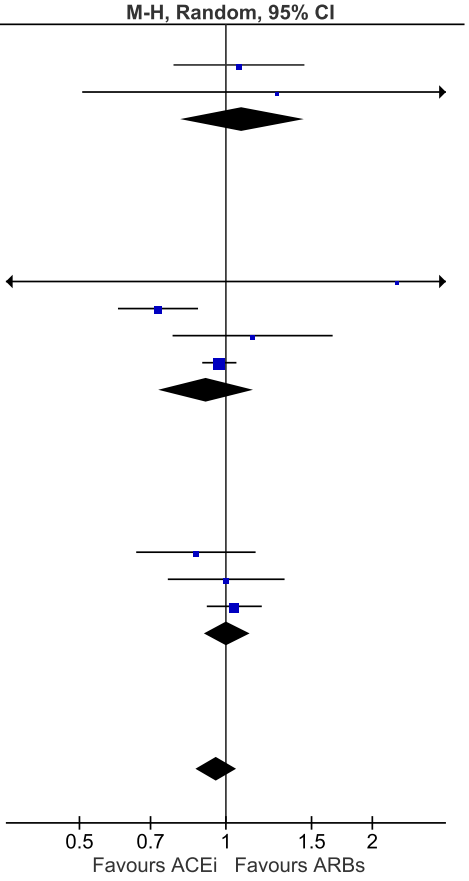
Fig. 2 (continued)

Conclusion

Overall, ACE inhibitors and ARBs had neutral effects on the odds for SARS-CoV-2 infection, admission to hospital, severe or critical illness, admission to ICU, or SARS-CoV-2-related death. However, subgroup analysis revealed differences among different continents; as in Asian countries, they decreased the odds for severe or critical illness and death, while in North America and Europe, they increased the odds for ICU admission and death, respectively. No differences were detected between ACE inhibitors and ARBs, except marginally insignificant protection with the use of ACE inhibitors towards SARS-CoV-2-related death. Collectively, the findings of the present meta-analysis challenge the

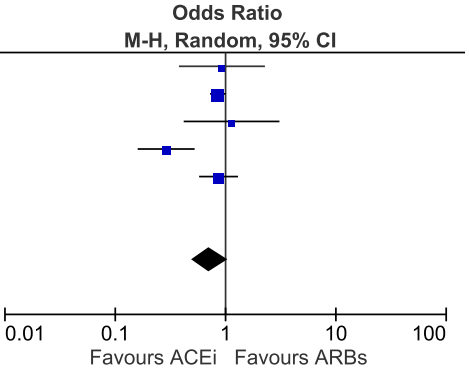
a

Study or Subgroup	ACEi Events	ACEi Total	ARBs Events	ARBs Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.1 Asia						
Huh 2020	46	653	668	10045	7.8%	1.06 [0.78, 1.45]
Yan 2020	5	560	53	7538	1.1%	1.27 [0.51, 3.20]
Subtotal (95% CI)		**1213**		**17583**	**8.9%**	**1.08 [0.81, 1.45]**
Total events	51		721			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.59)						
2.1.2 Europe						
Dauchet 2020	4	12	2	11	0.2%	2.25 [0.32, 15.76]
deAbajo 2020	240	2432	244	1860	15.4%	0.73 [0.60, 0.88]
Khawaja 2020	86	33827	39	17402	5.6%	1.13 [0.78, 1.66]
Mancia 2020	1502	8071	1394	7304	29.3%	0.97 [0.89, 1.05]
Subtotal (95% CI)		**44342**		**26577**	**50.6%**	**0.91 [0.73, 1.14]**
Total events	1832		1679			
Heterogeneity: Tau² = 0.03; Chi² = 9.47, df = 3 (P = 0.02); I² = 68%						
Test for overall effect: Z = 0.78 (P = 0.43)						
2.1.3 United States of America						
Mehta 2020	116	1322	98	982	9.0%	0.87 [0.65, 1.15]
Rentsch 2020	169	1011	94	563	9.3%	1.00 [0.76, 1.32]
Reynolds 2020	627	2088	664	2274	22.2%	1.04 [0.91, 1.19]
Subtotal (95% CI)		**4421**		**3819**	**40.5%**	**1.01 [0.90, 1.12]**
Total events	912		856			
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
Total (95% CI)		**49976**		**47979**	**100.0%**	**0.96 [0.87, 1.05]**
Total events	2795		3256			
Heterogeneity: Tau² = 0.01; Chi² = 12.80, df = 8 (P = 0.12); I² = 38%						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Chi² = 0.91, df = 2 (P = 0.63), I² = 0%						



b

Study or Subgroup	ACEi Events	ACEi Total	ARBs Events	ARBs Total	Weight	Odds Ratio M-H, Random, 95% CI
Benelli 2020	11	50	14	60	12.4%	0.93 [0.38, 2.27]
Khera 2020	319	2361	345	2226	32.4%	0.85 [0.72, 1.00]
Li 2020	7	35	15	83	10.7%	1.13 [0.42, 3.08]
Mehra 2020	16	770	38	556	19.3%	0.29 [0.16, 0.52]
Rossi 2020	56	450	52	368	25.2%	0.86 [0.58, 1.30]
Zhou 2020	0	0	0	0		Not estimable
Total (95% CI)		**3666**		**3293**	**100.0%**	**0.72 [0.49, 1.07]**
Total events	409		464			
Heterogeneity: Tau² = 0.12; Chi² = 12.50, df = 4 (P = 0.01); I² = 68%						
Test for overall effect: Z = 1.61 (P = 0.11)						



c

Study or Subgroup	ACEi Events	ACEi Total	ARBs Events	ARBs Total	Weight	Odds Ratio M-H, Random, 95% CI
Benelli 2020	4	50	9	60	24.7%	0.49 [0.14, 1.71]
Ebinger 2020	5	31	13	41	27.0%	0.41 [0.13, 1.32]
Mehta 2020	28	116	20	98	48.3%	1.24 [0.65, 2.38]
Total (95% CI)		**197**		**199**	**100.0%**	**0.73 [0.35, 1.56]**
Total events	37		42			
Heterogeneity: Tau² = 0.20; Chi² = 3.52, df = 2 (P = 0.17); I² = 43%						
Test for overall effect: Z = 0.80 (P = 0.42)						

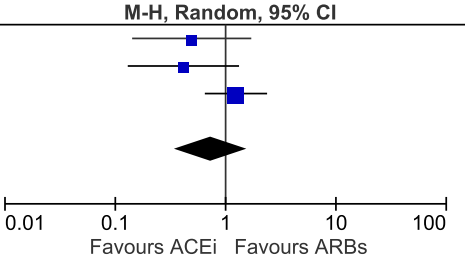


Fig. 3 **a** Odds for SARS-CoV-2-positive testing, **b** odds for admission to ICU, and **c** odds for SARS-CoV-2-related death, for ACE inhibitors users compared with ARBs users

recommendations of American and European Scientific Associations on the use of RAS inhibitors in the COVID-19 era. However, as all studies that were included in our analysis were observational, well-designed, randomized, controlled studies are needed to confirm or oppose these results.

Authors' Contribution MD conceived and designed the study. DP and AK performed the scientific literature search. DP and AK did literature screening. DP, AK, and KS extracted data and performed quality assessment of the included studies. DP did the analyses. DP and AK wrote the first draft of the report. MD, DP, KI, and MK contributed to interpretation and edited the draft report. All authors approved the final form of the paper before submission.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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